

*Remarks*

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-9, 11, 12, 14, 15, 17, 18, 20, 37-40, 43, 44, 47-48 and 50-82 are pending in the application, with claims 1, 2, and 47 being the independent claims. Claims 45, 46, and 49 have been canceled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue the canceled subject matter in a continuing application. Claims 1, 2, 5, 11, 12, 14, 15, 17, 18, 20, 37, 44, 47, 50, 55-61, and 63 have been amended, and claims 65-82 have been added. Support for the claim amendments and additions can be found throughout the specification (*e.g.*, page 5, lines 9-25; page 19, lines 17-28; page 20, lines 1-9; and pages 51-53).

It is believed these changes introduce no new matter. Their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and request that they be withdrawn.

*Formal Drawings*

Applicants thank the Examiner for indicating that the formal drawings have been accepted.

***Information Disclosure Statement***

Applicants request consideration of the IDS filed November 14, 2002, and making the documents listed therein of record in the present application.

***Objections to the Claims***

Claims 45 and 46 were objected to for being duplicates of claims 7 and 9, respectively. *See* OA at p. 3. Applicants have canceled claims 45 and 46. The objection therefore is moot, and Applicants respectfully request that it be withdrawn.

***Rejections Under 35 U.S.C. § 112, Second Paragraph***

Claim 5 was rejected as being indefinite for its recitation of the phrase “mutants and fragments thereof.” The Examiner asked “[w]hen does one DNA polymerase cease to be a mutant of one DNA polymerase and become a mutant of a different DNA polymerase?” OA at p. 3. Applicants respectfully traverse this rejection.

The principle inquiry under 35 U.S.C. § 112, second paragraph, is whether a person of ordinary skill in the art would be apprised of the scope of the claim. *See Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379 (Fed. Cir. 2000). The terms “mutant” and “fragment” are well known and clearly understood terms in the biotechnology field, and as such reasonably convey the scope of the claims to skilled artisans in the field. In response to the Examiner’s query, Applicants submit that those of ordinary skill in the art would understand a polymerase to be a mutant of one polymerase and not another polymerase based on relative sequence homology. Thus, a skilled artisan would understand a polymerase to be a mutant of polymerase X and not polymerase Y if

it is more homologous to polymerase X than to polymerase Y. Given the definitiveness of such sequence homology comparisons, those skilled in the art clearly would be apprised of the scope of the present claims. Applicants therefore respectfully request that this portion of the rejection be withdrawn.

Claims 5, 44, 50, and 63 were rejected for not further limiting claims 1 and 47, from which they ultimately depend. The Examiner asserted that “the listed DNA polymerases are not modified ... and thus claims 5, 44, 50 and 63 do not further limit claims (claims 1 and 47) from which they ultimately depend.” OA at p.4. Applicants respectfully traverse this rejection.

Claims 5, 44, 50, and 63 ultimately depend from, and therefore include all the limitations of claims 1 and 47, respectively. *See* 35 U.S.C. § 112 ¶ 3 (“A claim in dependent form shall be construed to incorporate by reference all the limitations all the limitations of the claim to which it refers”). Thus, it is implicit in claims 5, 44, 50, and 63 that the polymerase contains a modification specified in claims 1 and 47. Applicants therefore respectfully request that this portion of the rejection be withdrawn.

Claims 12, 14, 15, 17, 18, 20, and 56-61 were rejected for reciting “R (Arg722)” or “K (Lys726).” *See* OA at p. 4. Applicants have amended claims 12, 14, 15, 17, 18, 20, and 56-61 to omit the objectionable phrase. This portion of the rejection therefore is moot, and Applicants respectfully request that it be withdrawn.

Claims 11 and 55 were rejected for reciting “the O-helix of said polymerase.” The Examiner asserted that “it is unclear what is considered the O-helix.” OA at p. 5. Applicants respectfully traverse this rejection.

To clarify what is meant by the “O-helix,” claims 11 and 55 have been amended to recite “the O-helix of said polymerase corresponding to RXXXXXXXFXXXYYX (SEQ ID NO:1).” Applicants therefore respectfully request that this portion of the rejection be withdrawn.

***Rejection Under 35 U.S.C. § 112, First Paragraph***

Claims 1-9, 11, 12, 14, 15, 17, 18, 20, 37-40, 43, 45-62, and 64 were rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter that was not described in such a way as to reasonably convey to one of ordinary skill in the art that the inventors had possession at the time the application was filed. *See* OA at p. 6.

The Court of Appeals for the Federal Circuit (“Federal Circuit”) has provided substantial guidance regarding the written description requirement of 35 U.S.C. § 112 and satisfaction of the “possession test.” The Federal Circuit has instructed that that compliance with the written description requirement is to be assessed from the viewpoint of one of ordinary skill in the art. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (“the applicant must ... convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention”). The Federal Circuit also has instructed that compliance with the written description requirement does not require a patent specification to describe exactly the claimed subject matter; rather the specification must show the skilled artisan that the applicant invented what is claimed. *See Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, (Fed. Cir. 2000) (“The written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must

clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed”(citations omitted)). The Federal Circuit also has instructed that “[t]he disclosure rule does not require a particular form of disclosure.” *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321 (Fed. Cir. 2003). Relative to biotechnology inventions, the Federal Circuit instructed that functional descriptions of biological material can satisfy the written description requirement if a structure / function correlation is known in the art. *See Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003) (“Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.” (citation omitted)). Finally, the Federal Circuit has instructed that a specification that teaches one of skill in the art to make and use an invention can be sufficient to show a person of ordinary skill in the art that the inventor possessed the invention. *See Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321 (Fed. Cir. 2003) (“the specification that taught one of skill in the art to make and use an invention also convinced that artisan that the inventor possessed the invention.”).

Measured according to the Federal Circuit’s extensive instructions, Applicants’ specification fully supports the currently pending claims. Applicants’ specification allows those of skill in the art to recognize that Applicants invented what is claimed.

The Examiner asserted that Applicants’ specification does not comply with the written description requirement of § 112 present because “skilled artisans may not be able to determine those amino acids which correspond to Arg722 or Lys726 for many of

the modified polymerases of the claimed genus, much less be able to modify these amino acids such that the modification results in the desired activity.” OA at p. 7. The Federal Circuit has instructed specifically that this line of reasoning simply is not relevant to compliance with the written description requirement of § 112. *See Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003) (“The written description inquiry ... focuses on a comparison between the specification and the invention referenced by the terms of the claim--*not comparison between how the product was made as disclosed in the patent and future developments of this process that might alter or even improve how the same product is made.*” (emphasis added) (quoting the district court opinion with approval).

In any case, Applicants respectfully submit that Applicants’ specification does in fact teach those of skill in the art to make and use the claimed invention, and that such teaching clearly allows such persons to realize that Applicants possessed the invention. The Examiner recognized that Applicants’ specification has “exemplified how to generate mutations of a Tne polymerase for enhanced fidelity, reduced 3’-5’ and or 5’-3’ exonuclease activities, and/or reduced discriminatory activity against dideoxynucleotides.” OA at pp 6-7. Applicants’ specification also provides extensive guidance for generating corresponding mutations in other polymerases, and for determining the properties (*e.g.*, fidelity, exonuclease activities) of such mutated polymerases. *See, e.g.*, specification at p. 13, line 5 to p. 25, line 3. As Applicants’ specification points out, such exercises can be accomplished as a matter of routine experimentation those skilled in the art certainly can accomplish. As discussed above, the Federal Circuit has instructed that a specification that teaches one of skill in the art to

make and use an invention can be sufficient to show a person of ordinary skill in the art that the inventor possessed the invention. Thus, in view of the extensive “make and use” teachings in Applicants’ specification, persons skilled in the art certainly would recognize that the Applicants invented the claimed invention.

The Examiner also asserted that Applicants’ specification provides “no disclosure of any particular structure to function/activity relationship for the claimed genus.” OA at p. 7. This simply is not true. The Examiner admits that “applicants have disclosed the structural regions of the O-helix domain for a number of previously known DNA and RNA polymerases.” OA at p. 6. Applicants respectfully point out that because of the well-known correlation of polymerase structure and function, even this teaching is not required to meet the written description requirement of § 112. The Federal Circuit has stated, and the PTO has recognized, that the patent specification need only describe what is new or not conventional. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); MPEP 2163, p. 2100-165, col. 2 (Rev. 1, Feb. 2003).

Applicants respectfully submit that polymerase structure / function correlations were well-known in the art at the time the application was filed, and need not be reiterated in Applicants’ specification. It was well-known in the art that DNA polymerases and RNA polymerases are a highly conserved family of enzymes. In 1989, Wang et al. recognized the “striking similarity” between DNA polymerases of *E. coli*, phage, yeast, maize, herpes virus, vaccinia virus, and adenovirus. *See* Wang, T.S.-F. et al., *FASEB J.* 3:14-21 (1989).<sup>1</sup> In 1995, Arnold et al. recognized the “extensive similarity in overall architecture” between *E. coli* DNA polymerase I, HIV-1 reverse

transcriptase, T7 RNA polymerase, and rat DNA polymerase  $\beta$ . *See* Arnold, E. et al., *Current Opinion Struct. Biol.* 5:27-38 (1995).<sup>2</sup> And in 1996, Sousa, R. recognized that the DNA and RNA polymerases form a highly conserved family of nucleic acid polymerases. *See* Sousa, R., *TIBS* 21:186-190 (1996).<sup>3</sup> Sousa described DNA and RNA polymerases as modular enzymes “whose structural conservation often reflects common function.” *Id.* In addition, Sousa related these conserved motifs to three dimensional structure and function. *See id.* For example the polymerase domain, also referred to as a hand domain, carries out template-directed processive polymerization. *See id.* Other activities (*e.g.*, RNase H activity and exonuclease proofreading activity) are carried out by additional domains located in roughly the same position in the various polymerases. *See id.* As Sousa discussed, the conserved polymerase “hand” domain is composed of palm, fingers, and thumb subdomains. *See id.* The palm subdomain is responsible for carrying out phosphodiester bond formation. *See id.* Most of the palm subdomain, including Motifs A and C, are conserved throughout the family of polymerases. *See id.* Motifs A and C fold into three strands of a  $\beta$ -sheet and a short length of  $\alpha$ -helix. *See id.* Two amino acids in motifs A and C (corresponding to Asp705 and Asp882 in DNA polymerase I) align when polymerase structures are superimposed. *See id.* A third well conserved residue (corresponding to Asp186 in DNA polymerase I) also tends to align when polymerase structures are superimposed. *See id.* Motifs B and B' within the “fingers” are positioned similarly in relation to the active site in RNA-directed

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<sup>1</sup> Copy enclosed for the convenience of the Examiner.

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polymerases and DNA-directed polymerases. *See id.* The B motif contains the O-helix of DNA polymerase I. *See id.* The thumb subdomain is involved in processivity, and is an “extended, flexible, predominantly  $\alpha$ -helical” structure. *See id.* It inhibits polymerase dissociation by wrapping around and/or directly interacting with the template. *See id.*

As discussed above, functional descriptions of biological material can satisfy the written description requirement if a structure / function correlation was known in the art. The evidence clearly shows that nucleic acid polymerase structure / function correlations were known in the art by 1997, when the priority application for the present application was filed. As noted above, such well-known structure / function correlations need not be reiterated in Applicants’ specification.

Applicants also note that the present case is analogous to Example 16 in the PTO’s Synopsis of Application of Written Description Guidelines (“PTO Synopsis”). The hypothetical claim in Example 16 is drawn to an “isolated antibody capable of binding to antigen X.” *See* PTO Synopsis, p. 59. Example 16 also states that the specification contains an example in which antibodies against antigen X were “contemplated,” but not reduced to practice. *See id.* Although neither the hypothetical claim nor the specification in Example 16 recite any structure for the claimed antibody, the *PTO Synopsis* indicates that the specification meets the written description requirement of § 112. *See id.*, p. 60. Some of the reasons given are that: (1) methods for making antibodies were routine in the art, (2) antibody technology was well developed (e.g., the sequences of constant and variable regions of antibodies from a variety of species were published), and (3) antibodies have well defined structural characteristics. *See Id.*, pp. 59-60. Like Example 16, in the present situation, (1) methods of producing,

modifying and mutating DNA and RNA polymerases are routine, (2) the polymerase art is well developed, and (3) DNA and RNA polymerases have well defined structural characteristics.

Measured according to the Federal Circuit's extensive instructions and according to the PTO's guidelines, Applicants' specification clearly supports the currently pending claims. Applicants' specification clearly allows those of skill in the art to recognize that Applicants invented what is claimed. Based on the present specification, one of ordinary skill in the art would recognize that Applicants had possession of the claimed invention at the time the application was filed. Applicants therefore respectfully request that this rejection be withdrawn.

***Rejections Under 35 U.S.C. § 102***

Claims 1-4, 7, 11, 12, 14, 15, 17, 46-49, 52, 53, 55-59, and 64 were rejected under 35 U.S.C. § 102(b) for being anticipated by Astatke et al., *J. Biol. Chem.* 270:1945-1954 (1995). See OA at p. 8. Applicants respectfully traverse this rejection.

Currently pending claims 1-9, 11, 12, 14, 15, 17, 18, 20, 37-40, 43, 44, and 69-74 are directed to a nucleic acid polymerase comprising a modification that (b) increases or enhances fidelity and/or (b) reduces or eliminates misincorporation of nucleotides during nucleic acid synthesis, where the modification corresponds to amino acid position Arg722, or amino acid position Lys726, or amino acid positions Arg722 and Lys726, or amino acid positions Arg722 and Phe730 of a *Thermotoga neapolitana* polymerase, with the proviso that when the modification consists of a single amino acid substitution at either Arg722 or Lys726, said substitution is an amino acid other than Ala, and with the

proviso that when said modification comprises an amino acid substitution at Arg722, said substitution is an amino acid other than Pro, Trp, or Gln.

The Astatke reference does not teach, explicitly or inherently, or suggest polymerases having such properties and such combinations of mutations.

Claims 47-64 and 75-82 are directed to a thermostable nucleic acid polymerase comprising a modification that corresponds to amino acid position Arg722, or amino acid position Lys726, or amino acid positions Arg722 and Lys726, or amino acid positions Arg722 and Phe730 of a *Thermotoga neapolitana* polymerase, with the proviso that when the modification consists of a single amino acid substitution at either Arg722 or Lys726, said substitution is an amino acid other than Ala, and with the proviso that when said modification comprises an amino acid substitution at Arg722, said substitution is an amino acid other than Pro, Trp, or Gln.

The Astatke reference does not teach or suggest thermostable mutant polymerases having such combinations of mutations.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

***Conclusion***

All of the stated grounds of objection and rejection have been traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all currently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: 10/29/03

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